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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/828,700	04/21/2004	Chih-Chiang Yang	P464.312-0001	5387
<div>164      7590      09/20/2007 KINNEY &amp; LANGE, P.A. THE KINNEY &amp; LANGE BUILDING 312 SOUTH THIRD STREET MINNEAPOLIS, MN 55415-1002,</div>				
			<div>EXAMINER KRISHNAN, GANAPATHY</div>	
			<div>ART UNIT 1623</div>	<div>PAPER NUMBER</div>
			<div>MAIL DATE 09/20/2007</div>	<div>DELIVERY MODE PAPER</div>

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

**Office Action Summary**

Application No.

10/828,700

Applicant(s)

YANG ET AL.

Examiner

Ganapathy Krishnan

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 22 June 2007.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-6, 8-14 and 16-19 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-6, 8-14 and 16-19 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |                                                                                                            |                                                                                         |
|------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                                | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____                                                |

### **DETAILED ACTION**

The amendment filed 6/22/2007 has been received, entered and carefully considered.

The following information provided in the amendment affects the instant application:

1. Claims 7 and 15 have been canceled.
2. Claims 3, 5-6, 8-9, 11 and 13-14 have been amended.
3. Remarks drawn to rejections under 35 USC 112, second paragraph 102 and 103.

Claims 1-6, 8-14 and 16-19 are pending in the case.

#### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claims 6 and 14 for broad and narrow recitations and recitation of the term derivatives has been overcome by amendment. Regarding amended claims 6 and 14, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

The rejection of claims 7 and 15 has been rendered moot by cancellation of the claims.

The rejection of claims 3 and 11 has been overcome by amendment.

#### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

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(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The rejection of Claims 1-3 under 35 U.S.C. 102(b) as being anticipated by Bodor et al (Acta Pharm. Nord. 1989, 1(4), 185-193) is being maintained for reasons of record.

Applicants have traversed the rejection by arguing that the Examiner has based the rejection on the fact that the composition of Bodor is prepared in a manner similar to the method disclosed in Example 5 at page 13 of the instant specification and that instant Example 5 is a comparative example and that the actual working example is instant Example 6. This is not found to be persuasive. Instant Example 6 recites that the said composition was prepared as described in Example 5 by substituting free estriol with  $\beta$ -cyclodextrin complex of estriol.

Bodor teaches a composition comprising a cyclodextrin inclusion complex of 17-beta-Estradiol (steroidal active agent, estrogen) with 2-hydroxypropyl-beta-cyclodextrin and aqueous methanol (alcohol, limitation of claim 6) as the nonionic surfactant (noisome; page 186, first and second paragraphs; limitations of claims 1-3). According to Example 5 in the specification estriol and surfactant in ethanol are added to a water solution. In example 6 the cyclodextrin inclusion complex of estriol is used instead of free estriol. Since Bodor's example teaches the mixing of hydroxypropylcyclodextrin with a steroid (which would form the inclusion complex and this is added to methanol, a non-ionic surfactant) it is seen to produce the composition as instantly claimed. The instant claims are product-by-process claims, which are product claims. Applicants have not shown that the instant composition is different from that disclosed in the prior art. In Example 7 of the instant specification applicants state that the product of Examples 5 (as prepared by prior art method) and Example 6 (instant method) are niosomes. Hence the composition of Bodor should also produce a noisome.

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The rejection of Claim 19 under 35 U.S.C. 102(b) as being anticipated by Bodor et al (Acta Pharm. Nord. 1989, 1(4), 185-193) is maintained for reasons of record.

Bodor teaches a composition comprising a noisome as explained above. Bodor also teaches the effect of the cyclodextrin on the permeability of 17-beta-Estradiol through mouse skin (page 193, Table 4). It can be seen from Table 4 that permeation of 17-beta-Estradiol is enhanced (or facilitated) by using it in combination with 2-hydroxypropyl-beta-cyclodextrin and glycerol, another alcohol (non-ionic surfactant). This teaching is seen to meet the limitations of instant claim 19.

The following new art rejections are made of record necessitated by amendment

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 4-6 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bodor et al (Acta Pharm. Nord. 1989, 1(4), 185-193) in view of Siguroardottir et al (Drug Development And Industrial Pharmacy, 1994, 20(9), 1699-1078) of record and Heiber et al (US 5,212,199) newly cited.

Bodor teaches a composition comprising a cyclodextrin inclusion complex of 17-beta-Estradiol (steroidal active agent, estrogen) with 2-hydroxypropyl-beta-cyclodextrin and aqueous methanol (alcohol) as the nonionic surfactant (noisome; page 186, first and second paragraphs).

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The composition is prepared in a manner similar to the method as described in example 5 at page 13 of the instant specification and should produce a composition comprising a niosome as instantly claimed. Bodor, teaches the preparation of similar compositions using other steroidal active agents too (see page 186 under materials). However, Bodor does not teach compositions comprising the other cyclodextrins and the specific surfactants as instantly claimed.

Siguroardottir et al, drawn to similar compositions as Bodor, teach compositions comprising other nonionic surfactants like glyceryl monostearate, etc. (page 1701, last paragraph through page 1702, first paragraph).

Heiber drawn to skin permeation enhancers teaches compositions comprising a drug and sorbitan esters (non-ionic surfactant) for the said enhancement (col. 3, lines 12-18). One of the drugs that could be used in the composition is steroids (col. 5, line 15). One of skill in the art will recognize from this teaching that surfactants like glyceryl monostearate and Sorbian esters can be used in compositions for transdermal delivery of steroids. Heiber also discloses several other non-ionic surfactants that can be used in such compositions (col. 2, lines 1-57).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a composition comprising a niosome comprising the cyclodextrin derivatives and the surfactants as instantly claimed since the compositions comprising analogous active agents are seen to be taught in the prior art.

One of skill in the art would be motivated to make the compositions comprising the various active agents as instantly claimed since considerable amounts of hydroxypropyl beta cyclodextrin has been found to penetrate the skin barrier due to the action of surfactants and would look for other cyclodextrins and surfactant combinations that penetrate the skin barrier

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and hence help transport the steroidal active agent through the skin (Siguroardottir, page 1700, last paragraph). The use of non-ionic surfactants disclosed by Heiber (also as instantly claimed in claims 6 ) is seen to help in the permeation through the skin (col. 1, lines 15-60).

It is well within the purview of one of ordinary skill in the art to adjust ratios of the active agents in order to optimize the composition and extend the scope.

Claims 9-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bodor et al (Acta Pharm. Nord. 1989, 1(4), 185-193) in view of Loftsson (US 5,472,954) of record and Heiber et al (US 5,212,199) newly cited.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

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The instant claims are drawn to a method producing a composition if instant claim 1.

Bodor teaches a composition comprising a cyclodextrin inclusion complex of 17-beta-Estradiol (steroidal active agent, estrogen) with 2-hydroxypropyl-beta-cyclodextrin and aqueous methanol (alcohol) as the nonionic surfactant (as recited in instant claim 6; noisome; page 186, first and second paragraphs). The composition of Bodor is prepared by forming an inclusion complex of 17-beta-Estradiol (steroidal active agent, estrogen) with 2-hydroxypropyl-beta-cyclodextrin and then mixing the complex with a vesicle solution of the alcohol (non-ionic surfactant). However, Bodor does not teach the mixing of the two solutions in a ratio of 1.0 to 25.0, drying of the resulting mixture, grinding of the cyclodextrin and the steroid or freeze-drying as instantly claimed. The composition is prepared in a manner similar to the method as described in example 5 at page 13 of the instant specification and should produce a composition comprising a noisome as instantly claimed (see also explanation above).

Heiber drawn to skin permeation enhancers teaches compositions comprising a drug and sorbitan esters (non-ionic surfactant) for the said enhancement (col. 3, lines 12-18). One of the drugs that could be used in the composition is steroids (col. 5, line 15). One of skill in the art will recognize from this teaching that surfactants like glyceryl monostearate and Sorbian esters can be used in compositions for transdermal delivery of steroids. Heiber also discloses several other non-ionic surfactants that can be used in such compositions (col. 2, lines 1-57).

Loftsson, drawn to cyclodextrin complexation, teaches lyophilization (freeze drying) and grinding of an analogous complex of cyclodextrin and cellulose derivative (col. 28, lines 45-54). One of ordinary skill in the art will recognize that the same process step can be used for the process as instantly claimed.



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It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a composition comprising a niosome via the steps as instantly claimed since the same process steps are taught in the prior art using similar active agents.

One of skill in the art would be motivated to use the process as instantly claimed since the process steps of the prior art involve simple steps involving mixing the active agents and are easy to carry out/manipulate.

It is well within the purview of one of ordinary skill in the art to adjust process parameters, ratios of the active agents and also substitute other cyclodextrins, surfactants in the process in order to optimize the process and extend the scope.

***Response to Applicants Arguments Regarding Rejections Under 35 USC 103(a)***

Applicants have traversed the rejection of instant claims 4-6 and 8-14 and 16-19 (as amended now) arguing that;

1. The composition of Bodor is prepared in a manner similar to the method disclosed in Example 5 at page 13 of the instant specification and that instant Example 5 is a comparative example and that the actual working example is instant Example 6.

2. Siguroardottir does not teach or suggest forming a niosome as instantly claimed.

3. Loftsson does not teach or suggest the instant method.

Applicants' arguments are not found to be persuasive.

Bodor's teaching has been explained above (see 102(b) rejection above). His composition is seen to be the same as the one instantly claimed. Siguroardottir is cited for the use of teaching the use of glyceryl monostearate as surfactant in compositions analogous to

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Bodor. Hence one of skill in the art would use surfactant like glyceryl monostearate in the compositions of Bodor since they are closely analogous and Bodor's compositions show enhanced transdermal permeation. Heiber teaches the use of several other non-ionic surfactants for transdermal delivery of drugs including steroids. Loftsson, drawn to cyclodextrin complexation, teaches lyophilization (freeze drying) and grinding of an analogous complex of cyclodextrin and cellulose derivative (col. 28, lines 45-54). One of ordinary skill in the art will recognize that the same process step can be used for the process as instantly claimed. Hence the combination of the prior art renders the instant invention obvious.

### ***Conclusion***

Claims 1-6, 8-14 and 16-19 are rejected

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

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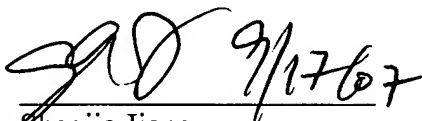
however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathy Krishnan whose telephone number is 571-272-0654. The examiner can normally be reached on 8.30am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

GK

  
Shaojia Jiang  
Supervisory Patent Examiner  
Art Unit 1623